REMARKS

Claims 1 and 15-20 are pending. Claims 21-22 are canceled. In view of the following remarks, reconsideration of the rejections is requested.

Restriction

The Office Action states that Claims 15-22 are directed to an invention that is independent or distinct from the invention originally claimed. It is stated that if these claims were originally presented they would have been restricted as distinct inventions. Applicants respectfully traverse and request reconsideration, and maintain the right to petition under 37 CFR 1.144. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal.

Applicants respectfully submit that the newly added claims are not directed to an invention that is properly restricted from Claim 1.

Specifically, Claims 18-19 are NOT drawn to the use of a second therapy for psoriasis. The claims merely provide alternative routes of administration for the claimed therapy, where one may select dermal administration or systemic administration. Applicants respectfully submit these alternative embodiments do not constitute an unreasonable burden to search, as the embodiments are closely related. 35 U.S.C. § 121, 37 C.F.R. § 1.141 and 37 C.F.R. § 1.142 all require that, for an application to be restricted, the alleged different inventions must be both independent **and** distinct. Applicants do not believe that a method of systemic administration of an ILK inhibitor, for example, is an independent and distinct invention from the base claim that recites the use of such an inhibitor without specifying the route of administration.

Claims 15-17 recite the use of a second therapy in addition to the therapy set forth in Claim 1. Applicants respectfully submit that the combination of a second therapy with the methods set forth in Claim 1 provide for an alternative embodiment of the main invention, and do not constitute an independent and distinct invention. These alternative embodiments do not constitute an unreasonable burden to search, as the embodiments are closely related.

Claim 20 recites the same method of treatment as Claim 1, i.e. administering an effective amount of an inhibitor of integrin linked kinase (ILK), wherein said ILK inhibitor is a small organic molecule that inhibits ILK activity. The essential feature of the claimed invention, which is a treatment of psoriasis with an effective amount of an ILK inhibitor, is the same in both Claim 1 and Claim 20. The difference between these claims is that Claim 20 specifically recites

a method step for determining whether expression of ILK in psoriatic tissue correlates with severity of disease. As such, Claim 20 is properly considered as an alternative embodiment within the genus of Claim 1, and is not an independent and distinct invention.

In view of the above remarks, Applicants respectfully request rejoinder of Claims 15-20 with Claim 1.

Priority

The Office Action has stated that the present claims, which are directed to methods of treating psoriasis with ILK inhibitors, are only given the current application filing date. Accordingly, Applicants have deleted the cross-reference to related applications, and submit herewith a substitute Application Data Sheet, which has deleted references to related applications.

Applicants note that the present application is assigned to QLT Inc., to Kinetek Pharmaceuticals, Inc. (as evidenced by the previously submitted certificate of Certificate of Amalgamation, Kinetek and QLT are merged), and to Sunnybrook and Women's College and Health Science Centre. The Office Action states that U.S. Patent no. 6,214,813 has no common inventors or assignees with the current application. However, the '813 patent is assigned to Kinetek Pharmaceuticals, Inc., and thus is commonly owned with the present application.

35 U.S.C. 112, first paragraph

The present claims have been rejected under 35 U.S.C. 112, first paragraph. Applicants respectfully submit that one of skill in the art could readily have practiced the present invention as claimed. The present application does not claim to have discovered methods or compounds for the inhibition of ILK, but rather utilize various methods known in the art for inhibition of this molecule, and apply these methods to the novel use of treating psoriasis.

Prior to the present invention, methods of utilizing small molecules to inhibit ILK activity were known and publicly available. One of skill in the art was informed as to assays, multiple model compounds, and guidelines for determining activity in a straightforward manner. The level of experimentation to select from among these known methods is routine, and readily performed by one of ordinary skill in the art.

In the present application, guidelines are providing for the selection of inhibitors, and for administration instructions, for example at paragraphs 52 and 56 – 69. Experimental models for inflammation are found at Examples 3 and 4, and for psoriasis in particular at Examples 1

and 2. The instant specification teaches the identification of integrin-linked kinase, specific compounds that inhibit the enzyme, and methods of screening for inhibitory agents, and methods of administration on pages 4-14. With respect to the working examples, the inhibitor MC-5 is 4-[(4-fluoro-3-trifluoromethylphenyl)hydrazono]-4H-pyrazole-3,5-diamine, a pyrazole compound, is shown to be effective in treatment of psoriasis. US Patent No. 6,214,813, referenced on lines 14-15 of page 5 of the present application, offers compounds with similar utility.

With respect to the state of the art at the time of filing, there were two patent applications issued in the US on small molecular ILK inhibitors, US Patent No. 6,214,813 issued April 10, 2001, US Patent No. 6,291,447 issued September 18, 2001; and US Patent No. 6,436,915, issued August 20, 2002. There is also a patent issued on inhibition with antisense constructs, US 6,177,273; and antibodies, US Patent No. 6,369,205 issued April 9, 2002.

Further ILK inhibitors may be found in U.S. Patent no. 7,022,702, issued April 4, 2006 and U.S. Patent no. 6,420,400 issued July 16, 2002, which describe 1,2,3-thiadiazole inhibitors. U.S. Patent no. 6,833,436, issued December 21, 2004, discloses short peptides that inhibit serine threonine kinases, including ILK.

High throughput screening techniques were well known at the time of filing, and high throughput screening for inhibitors of ILK have been described (See US Patent No. 6,214,813 columns 15-18). In addition, small molecule libraries were available for purchase from companies such as Talon Cheminformatics (Acton, Ontario) and Asinex (Moscow, Russia), providing a source of small molecules for screening.

In addition to the known inhibitors of ILK, screening programs using known methods have been shown to result in the identification of a number of inhibitors of ILK (for example those molecules described by U.S. 6,214,813 and U.S. 6,291,447). One skilled in the art could identify ILK inhibiting small molecules by running commercially available library compounds through an *in vitro* assay according to published techniques and calculating the IC_{50} using the methods provided in US Patent No. 6,214,813.

Methods that utilize inhibition of ILK have been widely published in the scientific literature. For example, one may look to Yau et al. (2005) Cancer Research 65:1497-1504, which tested the anticancer effects of ILK inhibitor QLT0254 in an orthotopic primary xenograft model of pancreatic cancer. Koul et al. (2005) Mol Cancer Ther. 4(11):1681-8 found that a newly developed small-molecule compound (QLT0267) effectively inhibited signaling through the ILK/Akt cascade in glioma cells by blocking the phosphorylation of Akt and downstream

targets, including mammalian target of rapamycin and glycogen synthase kinase-3beta. An anchorage-dependent cell growth assay confirmed the cell growth-inhibitory effect of QLT0267. Leung-Hagesteijn et al. (2005) Mol Cell Biol. 25(9):3648-57 demonstrated that treatment with a small molecule ILK inhibitor or expression of a dominant negative-acting ILK (ILK(E359K)) inhibited epithelial cell morphogenesis. Obara et al. (2004) Cancer Lett. 208(1):115-22 found that selective COX-2 inhibitor NS-398 was found capable of down-regulating ILK and PKB/Akt phosphorylation. Persad et al. (2000) Proc Natl Acad Sci U S A. 97(7):3207-12 showed that transfection of a kinase-deficient, dominant-negative form of ILK or exposure to a small molecule ILK inhibitor suppresses the constitutive phosphorylation of PKB/Akt on Ser-473, but not on Thr-308, in the PTEN-mutant prostate carcinoma cell lines PC-3 and LNCaP.

In summary, Applicants respectfully submit that small molecules that inhibit ILK were known and used in the art at the time of the present invention; and such molecules have subsequently been tested in a number of biologically relevant situations.

In the present application, data are presented that demonstrate an oral formulation was effective to reduce symptoms of psoriasis in animal models. In view of this evidence, and of the level of skill in the art regarding inhibition of integrin linked kinase, one of skill in the art could readily practice the claimed invention, with no more than routine formulation skill or experimentation. A person skilled in the art would be able to take the compounds disclosed in previously discussed US Patent No. 6,214,813, 6,291,447 and 6,436,915 (pryazoles) and 6,291,447 (granulatimides), as well as US Patent No. 6,001,622 (wortmannin) and U.S. Patent no. 7,022,702 (1,2,3-thiadiazoles) and apply them to the claimed method, using the information supplied in those patents and in the present application on pages 6-15 and 16-17.

The legal test for whether a disclosure provides adequate enablement for a generic claim, *e.g.* Claim 24, is that "the scope of the claims must bear a *reasonable correlation* to the scope of enablement provided by the specification to persons of ordinary skill in the art." *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. (BNA) 18, 24 (C.C.P.A. 1970) (emphasis added), *cited with approval in Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1212, 18 U.S.P.Q.2d (BNA) 1016, 1026 (Fed. Cir. 1991).

To evaluate the scope of enablement provided by a specification, the proper standard is whether any experimentation that may be needed to practice the claimed invention by the skilled artisan is undue or unreasonable. *In re Wands*, 858 F.2d at 736-37, 8 U.S.P.Q.2d (BNA) at 1404 (Fed. Cir. 1988). Whether a claim is enabled is a question of law based on underlying

factual findings. *Wands*, 858 F.2d at 735, 8 U.S.P.Q.2d (BNA) at 1402. *Wands* sets forth the relevant underlying fact inquiries:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. 858 F.2d at 737, 8 U.S.P.Q.2d (BNA) at 1404.

Thus, the requirement that the patent holder enable the "full scope" of the claimed invention has never been interpreted to require the enablement of every embodiment within the scope of the claims. *See, e.g., In re Wright*, 999 F.2d 1557, 1563, 27 U.S.P.Q.2d (BNA) 1510, 1515 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 U.S.P.Q.2d (BNA) 1438, 1445 (Fed. Cir. 1991) ("It is well settled that patent Appellants are not required to disclose every species encompassed by their claims, even in an unpredictable art.") (citation omitted); *Hormone Research Found. v. Genentech, Inc.,* 904 F.2d 1558, 1568, 15 U.S.P.Q.2d (BNA) 1039, 1047-48 (Fed. Cir. 1990); *Durel Corp.,* 256 F.3d at 1306, 59 U.S.P.Q. (BNA) at 1244 (accused product within scope of claims need not be enabled; patent is enabling even if it fails to enable a "significant percentage" of embodiments within the scope of the claims). In *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 750 F.2d 1569, 224 U.S.P.Q. (BNA) 409 (Fed. Cir. 1984), the court made clear that the full scope of a claim is enabled even if there are "significant" portions of the claim which are not enabled provided the person of ordinary skill can practice the invention without undue experimentation:

What is required is that "reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d at 1366, 42 U.S.P.Q.2d (BNA) at 1005 (Fed. Cir. 1997). According to *Novo Nordisk*, the essence of the enablement inquiry is that the inventor must teach how to make and use *the novel aspects of an invention*. *Id.*, 42 U.S.P.Q.2d (BNA) at 1005.

When determining the scope of enablement provided by an application, the law is clear that an enabling teaching may be provided "through broad terminology or illustrative examples." *In re Wright*, 999 F.2d at 1561, 27 U.S.P.Q.2d (BNA) at 1513; *see also In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. (BNA) 367, 369 (C.C.P.A. 1971). An express disclosure of only one illustrative example, such as a method of making one embodiment within the scope of the claimed invention, may be enough to enable the full scope of the claimed invention. *See Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1359-61, 47 U.S.P.Q.2d 1705, 1717 (Fed. Cir. 1998); *United States v. Telectronics, Inc.*, 857 F.2d 778, 786, 8 U.S.P.Q.2d (BNA) 1217, 1223 (Fed. Cir. 1988); *In re Wands,* 858 F.2d 731, 737, 8 U.S.P.Q.2d (BNA) 1400, 1407 (Fed. Cir. 1988).

To support a finding of non-enablement, the U.S. Patent and Trademark Office must establish a reasonable basis to question the enablement provided in the specification. *In re Wright*, 999 F.2d at 1562, 27 U.S.P.Q.2d (BNA) at 1513. The Office must not only explain why it doubts the statements in the specification's supporting disclosure, but also must support its assertions "with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d at 224, 169 U.S.P.Q. (BNA) at 370. The Office is required to consider the factual evidence in favor of enablement in the record. *In re Alton*, 76 F.3d 1168, 1175, 37 U.S.P.Q.2d (BNA) 1578, 1583 (Fed. Cir. 1996). When an applicant requests reasonable factual support for an Examiner's rejection, the Examiner must provide it under 37 C.F.R. § 1.104(d)(2). The Board is not obligated to accept as fact any statements of the Examiner that are not adequately supported in the record. *Application of Lundberg*, 244 F.2d 543, 551, 113 U.S.P.Q. (BNA) 530, 537 (C.C.P.A. 1957). Indeed, the Board should not accept as fact any of the Examiner's statements that lack support in the record. *Dickinson v. Zurko*, 527 U.S. 150, 154 (1999).

The present specification enables one of ordinary skill in the art to practice the method set forth in Claim 1. The consideration of Wands factors are as follows.

Wands Factor 1. Any experimentation required to have practiced the invention of claim 1 was quite low.

As discussed above, compounds for inhibition of ILK and methods for their use were known in the art at the time of filing the present application. One need only optimize dose and formulation for practice of the invention. As such, the only experimentation that may be required is to perform experiments to determine the appropriate dose of a certain activity. Since such experiments are empirical in nature, no undue experimentation is required.

Wands Factor 2. The specification provides significant guidance to the skilled worker for practicing the invention of Claim 1.

As discussed in detail above, one of skill in the art was well-informed as to inhibitors of integrin linked kinase at the time of filing the present application. Specific guidelines for the administration of such compounds is provided in the specification, for example at paragraphs 52 and 56 – 69. The instant specification teaches the identification of integrin-linked kinase, specific compounds that inhibit the enzyme, and methods of screening for inhibitory agents, and methods of administration on pages 4-14.

Wands Factor 3. The instant specification contains working examples that demonstrate embodiments of the invention claimed, including the actual cloning of human ILK and the use of the protein as an immunogen.

Experimental models for inflammation are found at Examples 3 and 4, and for psoriasis in particular at Examples 1 and 2. Therefore, it is demonstrated that treatment of psoriasis can be effected by administration of an integrin linked kinase inhibitor.

Wands Factor 4. The nature of the invention claimed is treatment of psoriasis.

Contrary to the statement made in the Office Action, the claims are not drawn to a method for treating chronic inflammation, but have been previously amended to specifically recite treatment of psoriasis.

Wands Factor 5. The state of the art in December 1995 was quite sophisticated.

As stated by the Patent Office on page 8 of the Office Action, "the state of the art regarding "a small organic molecule" and its subsequent testing as an inhibitor of ILK or any receptor is high."

Wands Factor 6. In November 2001, the level of skill in the art was high.

The routine level of skill in the field of recombinant nucleic acid technology in November 2001 was represented by a scientist with a Ph.D. degree and two years of post-doctoral training. Furthermore, such technicians are required to keep abreast of the latest technology through continuing education and reading of scientific journal articles. As such, the skill level of those developing and using methods for manipulating performing cell-based assays is high. Such a person would have considered it routine to select from available compounds or screen libraries of compounds using the common general knowledge, tools, and methods available in the field.

Wands Factor 7. Utilizing various known compounds or screening libraries of compounds against a known target using published methods was predictable.

The amount of experimentation required to treat psoriasis using compounds that specifically inhibit integrin-linked kinase, as identified by Applicants, would not be undue because a) examples of inhibitors are provided, b) guidance is given on how to screen for additional inhibitors, and c) one of skill in the art would be able to perform the experiments as a matter of routine to determine the optimal dosage.

Wands Factor 8. Breadth of Claims.

With respect to the breadth of the claims, the breadth is commensurate with the scope of the invention in light of what was previously known. It is believed that the applicant is entitled to this scope for this reason. Withdrawal of the rejection is requested.

It is the factual inquiries set forth in *In re Wands* that determine undue experimentation. Accordingly, the enablement of Claim 1 provided by the instant specification is reasonably commensurate with the scope of all the claims. See *In re Fisher*, 427 F.2d at 839, 166 U.S.P.Q. (BNA) at 24, *cited with approval in Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d at 1212, 18 U.S.P.Q. 2d (BNA) at 1026. The inventors have taught how to practice all the claimed features of their invention. See *W. L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d at 1557, 220 U.S.P.Q. (BNA) at 316.

In view of the above amendments and remarks, Appellants respectfully submit that the present claims meet the requirements of 35 U.S.C. 112, first paragraph with respect to enablement.

Claim 1 has been rejected under 35 U.S.C. 103 as being unpatentable over Bonjouklian *et al.*, U.S. Patent no. 5,378,725 in view of Zhang et al. (1999) Chinese Medical Journal 112:1097-1100.

Applicants respectfully submit that the presently claimed invention not made obvious by the cited art.

The present invention is based on the finding that the integrin linked kinase (ILK) is clearly correlated with the severity of psoriatic lesions, as shown in Figures 1 and 2. Prior to the instant invention it was unknown whether the activity or expression levels of ILK were altered in the specific human pathologic states resulting from psoriasis. Psoriasis is a complex inflammatory autoimmune condition characterized by an abnormal activation of skin T lymphocytes, dermal and epidermal infiltration by various types of leukocytes, hyper-proliferation of keratinocytes and pronounced angiogenic activity within the dermal vasculature.

As shown in Figure 1, a low level of ILK expression is seen in normal keratinocytes, and little or no ILK staining occurs in the dermal vascular endothelium. In contrast, staining for ILK was found to be highly intense for the hyper-proliferative keratinocytes within psoriatic plaques. Further, some of the inflammatory cells present within the dermal region stained positively for

ILK. Overall, in contrast to normal skin, ILK was expressed at much higher levels within the epidermal and dermal regions within skin plaques of patients with psoriasis.

The primary reference, US 5,378,725 teaches that wortmannin and analogs thereof are inhibitors of phosphatidylinositol 3-kinase. The '725 claims reflect this specificity, and are directed to methods of treating a phosphatidylinositol 3-kinase-dependent neoplasm in a mammal by administering to the mammal wortmannin or an analog thereof.

The reference fails to teach the association of integrin linked kinase with psoriasis, or the treatment of psoriasis with an inhibitor of integrin linked kinase.

The secondary reference fails to remedy the deficiencies of the primary reference. Zhang *et al.* states that there is an increase in expression of PI3-kinase in psoriatic lesions as evidenced by non-quantitative methods of immunohistochemistry, *in situ* hybridization, and dot blot analysis. The reference states that PI 3-kinase *may* be correlated with hyperproliferation of psoriatic keratinocytes, but that "further studies are required to elucidate it".

The reference fails to teach the association of integrin linked kinase with psoriasis, fails to teach the treatment of psoriasis with an inhibitor of integrin linked kinase, and even fails to teach the treatment of psoriasis by inhibition of PI3 kinase.

One of skill in the art could not reasonably expect to be in possession of the presently claimed invention based on the combination of cited references. Even assuming that there is an increase in PI3 kinase associated with psoriasis, the art does not teach that such an increase is associated with disease progress, or could be inhibited to provide treatment of psoriasis.

In view of the above remarks, Applicants respectfully submit that the present claims are not made obvious by the cited combination of art. Withdrawal of the rejection is requested.

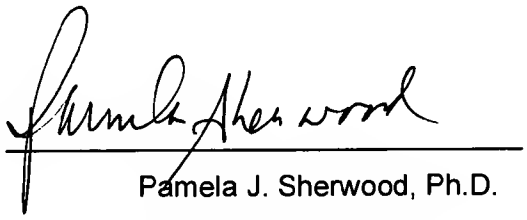
Conclusion

Applicants submit that all of the claims are now in condition for allowance, which action is requested. If the Examiner finds that a Telephone Conference would expedite the prosecution of this application, he is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any other fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number KINE-001CIP5.

Respectfully submitted,

Date: August 1, 2006

By: 

Pamela J. Sherwood, Ph.D.
Registration No. 36,677

Enclosure: Substitute Application Data Sheet

BOZICEVIC, FIELD & FRANCIS LLP
1900 University Avenue
East Palo Alto, CA 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231